U.S. FOOD & DRUG ADMINISTRATION

Bioequivalence Evaluation For Generic Drug Products -Discussion with PKWP-

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The slides are prepared to guide an informal discussion with EMA colleagues during my fellowship visit from Oct 16-26, 2018.

Key Objectives of My Fellowship

Learn EMA's approach on Generics and Hybrids

- Learn EMA's process and principles in developing guidelines related to generics include product-specific bioequivalence guidelines
- Understand possible reasons for the observed differences in BE recommendations

Explore a possible pilot project on complex generics using the Parallel Scientific Advice (PSA) mechanism

- Understand the PSA process, logistics, and timeline
- Establish connection
- Identify benefit and develop criteria for using this mechanism

Identify opportunities for future interaction and convergence

- Interact with the CPN group, PKWP, and QWP on guidance development for generics
- Create opportunities for global development of generics

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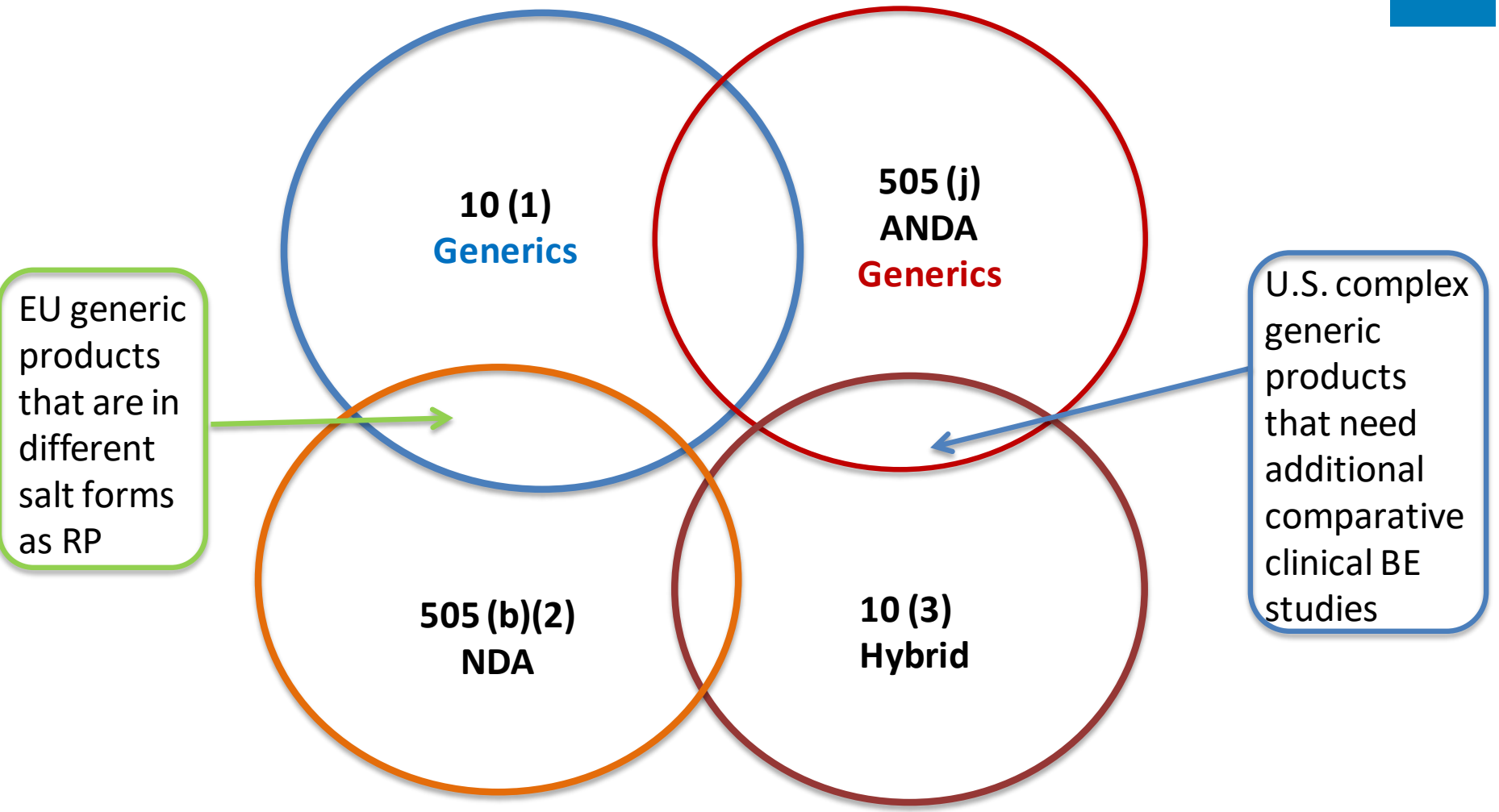
Approval Pathways

Four different routes for two broad categories of drug applications under the FD&C Act	
1.	Stand-alone new drug application (NDA) submitted under **505(b)(1)** and approved under 505(c)
2.	**505(b)(2)** NDA submitted under 505(b)(2) and approved under 505(c)
3.	Abbreviated new drug application (ANDA) submitted and approved under **(505(j))**
4.	**Petitioned ANDA** submitted under 505(j)(2)(C) and approved under 505(j)

Draft Guidance for Industry: Determining Whether to Submit an ANDA or a 505(b)(2) Application
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM579751.pdf

EMA vs. FDA

Abridged or Abbreviated Pathways for small molecule drugs



In the US, biologics and biosimilar are regulated by a different law. It is under Public Health Service (PHS) Act: 351 a and 351 k. At the FDA, biosimilar (351 k) products are reviewed by a different group under OND (the group will become a new office in CDER, that is a separate office from the OGD).

Basic Generic Drug Requirements

No Significant Differences from the RLD

- **PHARMACEUTICAL EQUIVALENCE:** the foundation of equivalence
  - Same active ingredient(s)
  - Same strength
  - Same dosage form
  - Same route of administration
- **Bioequivalence:** supports true pharmaceutical equivalence
  - absence of a significant difference in the **rate** and **extent** of absorption after administration
  - **available at the site of drug action** when administrated at the same molar dose under similar conditions

Allowed Difference in Generics

A generic product cannot have *significant differences.* These would include differences that would impact the safety or efficacy profile of the branded drug product (RLD). Generics may vary in the following, depending on the drug product:

- Shape
- Scoring configuration
- Release mechanism
- Packaging
- Excipients
- Buffers, Preservatives, Thickening Agents, Tonicity Adjusters (for Ophthalmic Products)
- Expiration dating
- Minor labeling differences
- Storage requirements

FDA General Guidances Related to BA and BE

- Two guidances, one for NDAs and one for ANDAs:
  - NDA: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations (3/2014)
    - "bioequivalence" will be removed from the title
  - ANDA: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application(12/2013)
    - RS/RLD, special population, new appendices
- Both guidances are under revision and new drafts will be published ~4Q2018.
- Dissolution are in separate guidances
  - Final guidance: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (12/2017)
  - Final guidance: Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances (8/2018)

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm

Bioequivalence Assessment for Immediate-Release Oral Dosage Forms

Key topic areas for discussion:

- Study design
  - e.g., crossover vs. parallel, subject (healthy vs. patients), sample size, fasting vs. fed, replicate vs. non-replicate design, dose strength to be studied, single dose vs. multiple dose
- Data analysis
  - e.g., statistical methods for BE assessment, handling of outlier data, average bioequivalence vs. scaled bioequivalence, analyte(s) to be measured and applied BE limit (parent vs. metabolite)
- Data interpretation and BE acceptance limit
- Provisions for waiving BE study requirements (i.e., granting biowaivers)
- Special considerations on other topics such as
  - Drugs with non-linear PK
  - Drugs with long half-life
  - Narrow therapeutic index (NTI) drugs
  - Highly variable (HV) drugs

Examples of Differences Between FDA and EMA For Oral Dosage Form BE Evaluation*

	FDA	EMA
BE Study Design		
IR	Both Fasting and Fed conditions	Fasting condition only
MR	Single dose	Single and steady-state
Data Analysis		
Highly Variable Drugs	Scaled can be done for both Cmax and AUC	Scaled for Cmax but not AUC
NTI drugs	NTI working group 5 criteria	Case-by-case, clinical considerations Tighter

***Differences in general BE guidance also lead to differences in PSGs for specific products.**

Specific to MR dosage form

FDA	EMA
• **Generally single-dose**, fasting & fed BE studies using the highest strength – Single-dose studies are usually considered to be more sensitive in detecting formulation differences • **Multiple dose BE studies** – When safety considerations suggest using patients who are already receiving the medication, often the only way to establish BE without disrupting a patient's ongoing treatment is in a steady-state study	• **Extended-release products** 1) No accumulation risk: single dose (+pAUCs) 2) With accumulation: single dose, multiple dose • **Multiphasic modified-release products** 1) No accumulation risk: single dose (+pAUCs) 2) With accumulation: single dose (+pAUCs), multiple dose • **Delayed-release products** Single dose

FDA guidance: Bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an ANDA
EMA guidance: Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms

PSG Example: Paliperidone ER tablets

	FDA	EMA
Dose	1.5 mg, 3 mg, 6 mg, 9 mg, and 12 mg* *12 mg dose – Discontinued "Federal Register determination that product was not Discontinued or withdrawn for safety and efficacy reasons	1.5 mg, 3 mg, 6 mg, 9 mg, and 12 mg
BE study design	• **Single dose fasting**: 6 mg[a]; Healthy males and nonpregnant females, general population • **Single dose fed:** 6 mg; Healthy males and nonpregnant females, general population	• **Single dose fasting** : all strength or bracketing, healthy volunteers • **Single dose fed:** 12 mg, healthy volunteers • **Multiple dose fasting:** highest tolerable strength in healthy volunteers or highest strength in patients
BE assessment	AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}	• **Single dose:** AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} • **Multiple dose:** $AUC_{0-\tau}$, $C_{max,ss}$, and $C_{\tau,ss}$
Others	Waiver request of in vivo testing: 1.5 mg, 3 mg, and 9 mg based on (i) acceptable bioequivalence (BE) studies on the 6 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths	

[a] The 6 mg strength is recommended for BE study considering the safety of study subjects and considering that it is the recommended starting dose

Bioequivalence Study Design Tailored for Different Drug Products (FDA Approaches)

Types of Drugs	Study Design	Sequence	BE criteria	
			Mean comparison	Variability comparison
Non-NTI, Non HVD drugs	Single-dose 2-way crossover	T, R R, T	Yes, CI 80.00-125.00%	No
HVD drugs	Single-dose, partially replicated, 3-way crossover Single-dose, fully replicated 4-way crossover	T, R, R R, R, T T, R, T, R R, T, R, T	Yes, CI scaled, point estimate constraint	No
NTI drugs	Single-dose, fully replicated, 4-way crossover	T, R, T, R R, T, R, T	Yes Must pass both the reference scaled limits and the unscaled average bioequivalence limits of 80.00-125.00%.	Yes The upper limit of the 90% CI of the ratio of the within-subject standard deviation of the test to reference product is less than or equal to 2.5.

FDA's ICH Reflection Paper

- ICH Management Committee sent the paper to the ICH Assembly
- ICH Assembly is currently reviewing the paper, and it will be discussed on 11/14 or 11/15
- If the paper is endorsed
  - Informal discussion group will be formed
- Will submit a new topic proposal to ICH in December
  - Initial focus: non-complex IR oral dosage form
  - Slide 8

FDA Commissioner's Blog on Generic Drug Harmonization October 18, 2018

FDA

FDA Voices

- FDA Voices on Policy
- FDA Voices on Consumer Safety and Enforcement
- FDA Voices on Medical Products
- FDA Voices on Food
- FDA Voices on Tobacco

Advancing Toward the Goal of Global Approval for Generic Drugs: FDA Proposes Critical First Steps to Harmonize the Global Scientific and Technical Standards for Generic Drugs

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October 18, 2018

By: Scott Gottlieb, M.D.

Too many Americans struggle with the high cost of drugs. In some cases, patients go without needed medicines. This is why drug pricing is a matter of public health. And it's why FDA launched a Drug Competition Action Plan that focuses on three key areas designed to facilitate more generic competition, promote patient access, and improve the economics of developing generic medicines.

While we've made substantial progress in fostering more competition by resolving obstacles that can make it difficult to win approval of generic versions of certain complex drugs, increasing the speed of generic approvals, and closing down ways that branded companies game the system to prolong drug monopolies, there's still more work to be done.

So we're opening up some new policy fronts when it comes to our Drug Competition Action Plan. And we're re-launching that plan for 2019 with some additional initiatives. Chief among them is a new effort that FDA has proposed to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), a key international body comprised of other regulatory authorities and the pharmaceutical industry: The pursuit of common global development standards for generic drugs.

FDA Commissioner Scott Gottlieb, M.D.

https://www.fda.gov/NewsEvents/Newsroom/FDAVoices/ucm623665.htm

Complex Generic Products -Cornerstone of GDUFA II

- Complex active ingredients
  - Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
  - Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
  - Locally acting such as dermatological and inhalational drugs
- Complex dosage forms
  - Long acting injectables and implantables, transdermals
- Complex drug-device combinations
  - Nasal sprays, metered dose inhalers, dry powder inhalers
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement
  - Opioids with abuse deterrent formulations

GDUFA: Generic Drug User Fee Amendments; API: Active Pharmaceutical Ingredient

https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Complex Products

A defined term in the GDUFA II Commitment Letter

COMPLEX…	Example	Example Products
Active ingredients	Peptides, complex mixtures, natural source products	Glatiramer acetate
Formulations	Liposomes, emulsions	Liposomal formulation
Routes of Delivery	Locally acting drugs such as dermatological products and complex ophthalmological products	Acyclovir cream
Dosage Forms	Transdermal systems, extended release injectables	PLGA microspheres
Drug-Device Combinations	Dry powder inhalers, nasal sprays, transdermal systems	Mometasone Nasal Spray
Other products	Complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement	Abuse deterrent opioid formulations

Generic Drug User Fee Amendment (GDUFA) II Commitment Letter: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Complex or Non-Complex Products?

Non-complex

- Tablet, capsules, solutions and suspension for oral administration and systemic delivery
  → Solid oral modified-release (MR) dosage forms are non-complex
- Solutions for topical or parenteral administration

Complex

- Complex active ingredients including peptides
- Complex dosage forms (e.g., long acting injectable, transdermal systems)
- All locally acting drugs
- Drug-device combinations with user interface considerations
- Abuse deterrent formulations

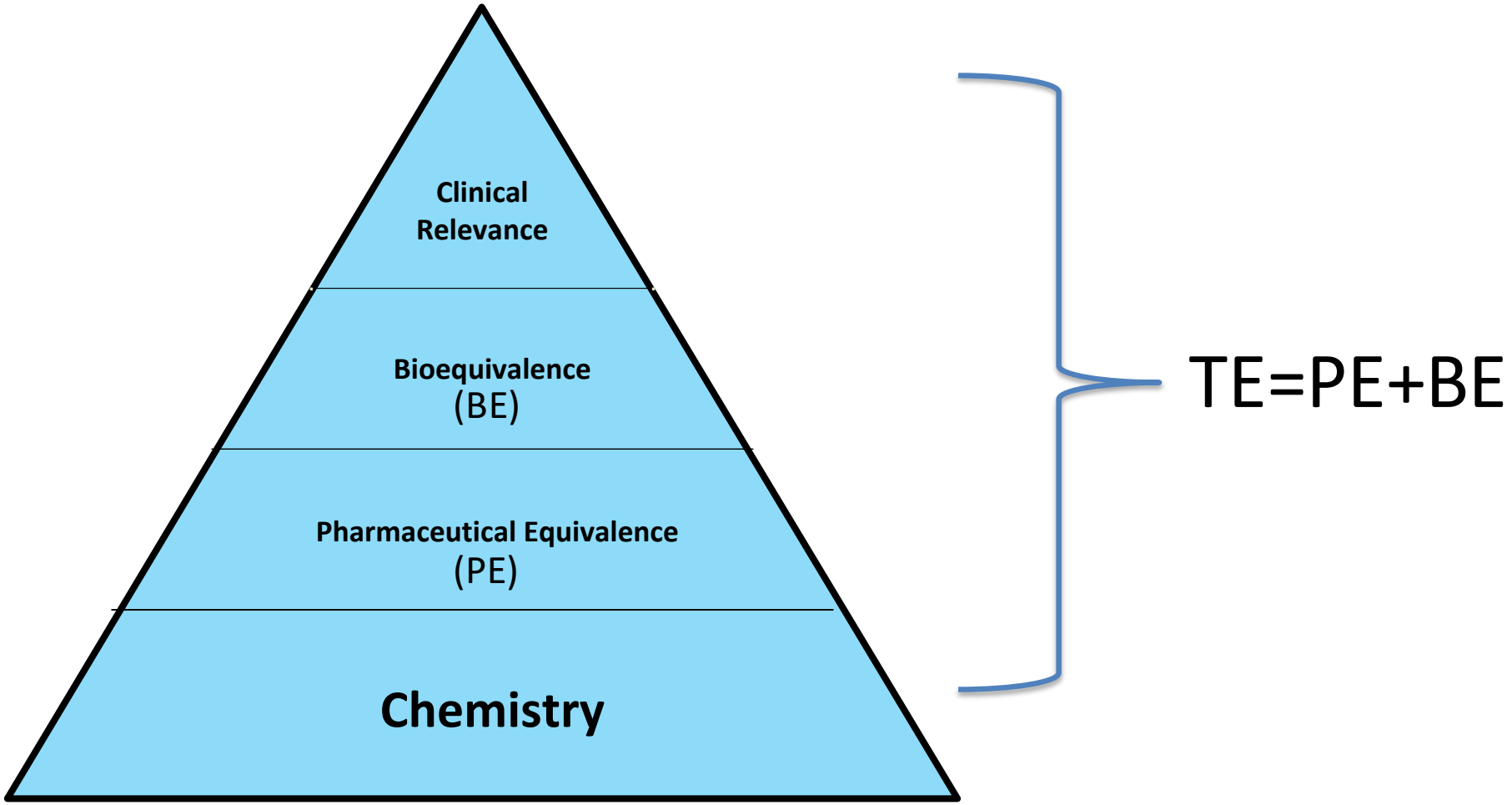
Generic Drug User Fee Amendment (GDUFA) II Commitment Letter:
https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Pre-ANDA Program for Complex Products: Product-Specific Guidances (PSGs)

For NCE Products (non-complex)	For Complex Products	For Other Products
• FDA will issue PSGs for 90% of NCE NDAs approved on or after October 1, 2017, at least 2 years prior to the earliest lawful ANDA filing date	• There are Pre-ANDA meetings for complex products without a PSG or guidance • FDA will strive to issue PSGs for complex products as soon as scientific recommendations are available	• Based on requests from the regulated industry and public health priorities

NCE: New Chemical Entity; NDA: New Drug Application

Evaluations of Generic Drugs



Developing Methods to Support BE Evaluation

- Q1, Q2, Q3 approaches
  - Qualitative, quantitative and physicochemical sameness
- In vitro testing (Q3) Methodologies
  - Release testing
  - Permeation
  - Raman spectroscopy
  - Computational fluid analysis
  - Microsampling strategies
  - Others
- Improved Study Design

  (directly the result of better understanding of drug product performance attributes)
- Modernized Statistical approaches
- Clinical Pharmacology tools
  - Modeling
  - Simulation

ALL WITH THE INTENT TO…..
compile and align orthogonal evidence to conclude "Sameness"/Equivalence

Source:
See Slide 29 for a list of FDA workshops on complex generic drug products

Product Specific Guidances for Generic Drugs (PSGs)

- Represent FDA's thinking and expectations on the appropriate methodology and evidence needed to support generic drug approval
- Highly utilized by the public and FDA
  - Foster and support generic drug development
  - Support FDA's ANDA review
- Since 2007, there are >1,600 PSGs published
  - ~400 (25%) are for complex products
  - Batch 21 published on Sept 13, 2018 and a "stand-alone" batch of 25 TDS PSGs (2 new and 23 revisions) on Oct 9, 2018
- Publish on a quarterly basis (~40-50/batch)
- Also publish "stand-alone" batches
- PSGs not just focus on BE recommendation, also contain
  - In vitro equivalence evaluation (particle size, etc)
  - In vitro dissolution

PSG Process

Sources:
- Newly approved NDAs (Orange Book and Drug@FDA)
- Submitted ANDAs
- Public requests
- FDA internal requests /needs

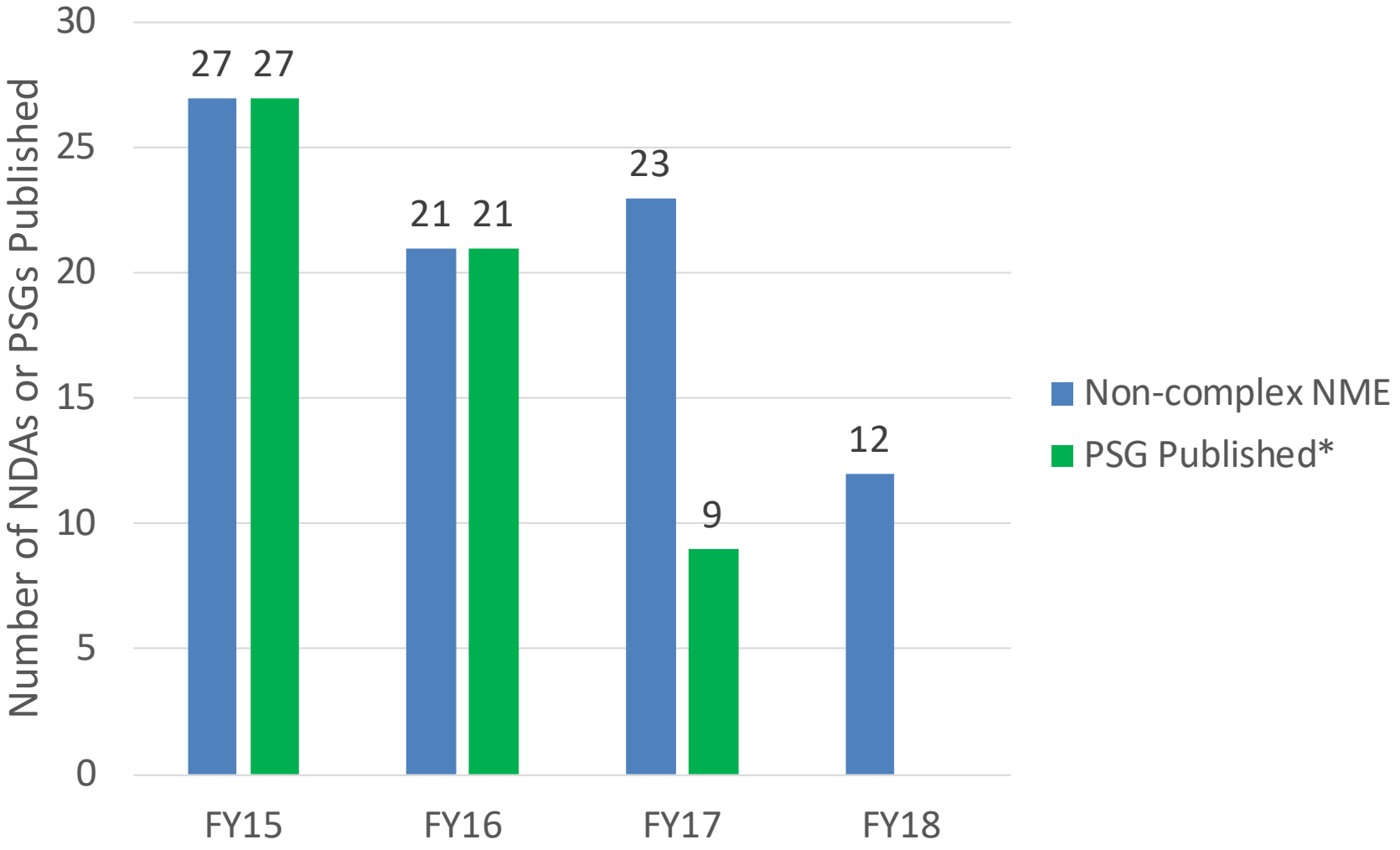
Consider Research

ANDA Review Team (OGD, OPQ)

Identify → Prioritize → Develop → Undergo Clearance → Publish

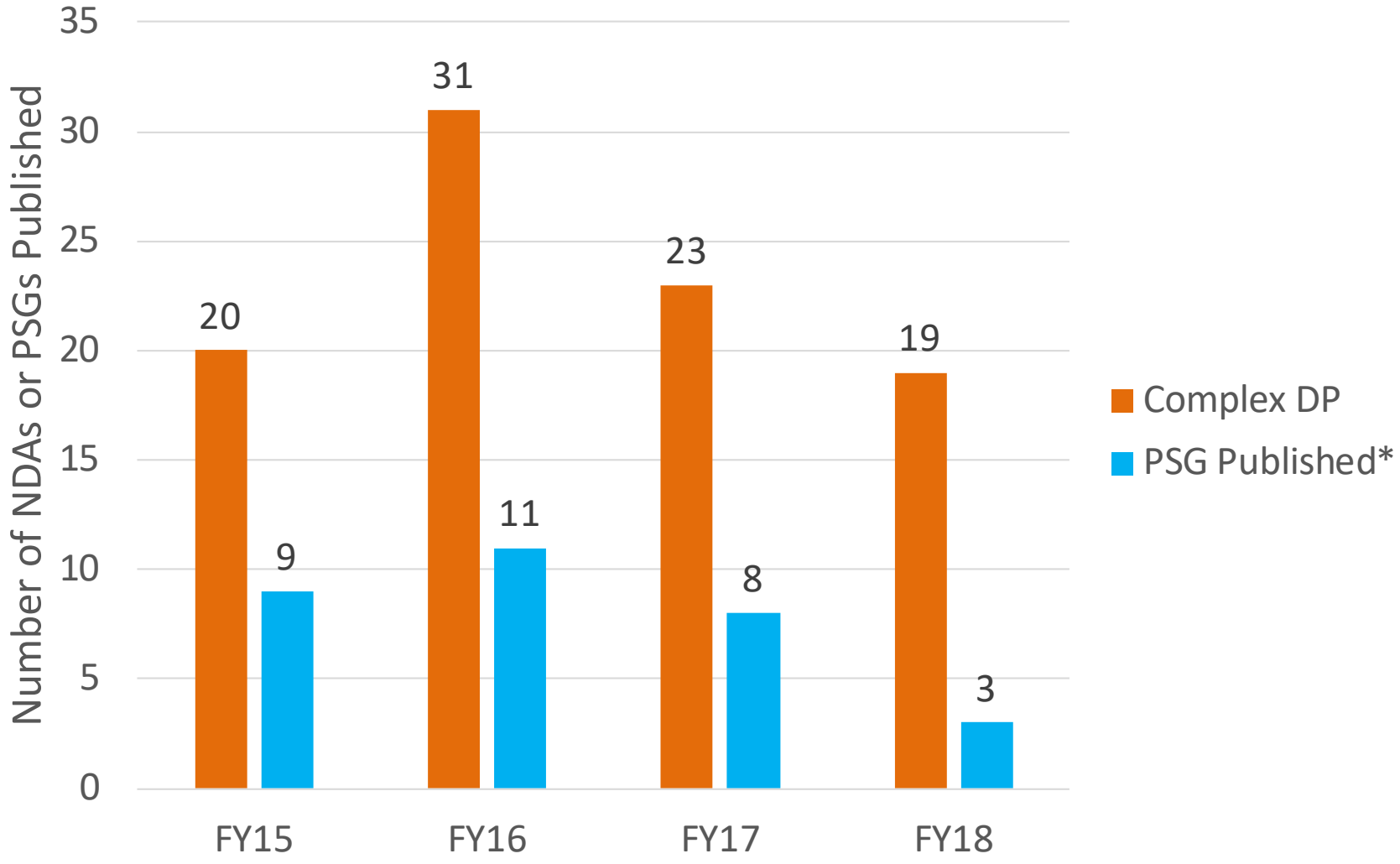
Criteria considered include:
- Non-complex NMEs (2 years after approval)
- Complex NMEs
- Top 50 complex products w/o approved ANDA
- Complex products with in-house ANDA
- Newly approved NDAs
- In-house ANDAs w/o PSG
- Drug shortage or price fluctuation
- Pre-ANDA meeting request
- Citizen petition

Product-Specific Guidance (PSG) Development for Recent Non-complex NMEs



* Number includes PSG published and drug products may be eligible for "biowaiver" under 21 CFR 320.22(b)

PSG Development for Recent Complex Drug Products



* Number includes PSG published, drug products that are covered under FDA general guidance and may be eligible for "biowaiver" under 21 CFR 320.22(b)

Differences in PSGs-EMA Batch 9

Drug Name	Major difference between FDA vs EMA recommendation (besides general fasting and fed study considerations)	Potential discussion points with EMA
Apixaban	FDA recommends fast and fed study in healthy males and non-pregnant females + in vitro comparative nasogastric tubing study EMA recommends one fasting study with intact tablet and one with crushed tablet in healthy volunteers (crushed study can be waived if scientifically justified)	EMA guidance end of consultation 1. Rationales for not including crushed tablet study 2. In vitro comparative nasogastric tubing study requirements
Gefitinib	FDA recommends fasting and fed studies in healthy male + in vitro comparative nasogastric tube studies EMA recommends fasting study in healthy volunteers (no gender differentiation), AUC_{0-72} + in vitro study as dispersion in water and as dispersion through a NG tube	EMA guidance end of consultation 1. Gender consideration for subject selection 2. Consistency regarding the requirement for in vitro NG study
Lapatinib	EMA recommends single dose fasting and fed studies in healthy volunteers FDA recommends steady state study in patients	EMA guidance End of consultation 1. Heathy subject vs patient selection

Follow up from Wenlei's visit in April 2018 (last PKWP meeting discussion)

Differences in PSGs-EMA Batch 9

Drug Name	Major difference between FDA vs EMA recommendation (besides general fasting and fed study considerations)	Potential discussion points with EMA
Pegylated liposomal doxorubicin HCl	The only remaining difference between FDA and EMA is that EMA recommends pAUC0-48 and pAUC48-last	EMA guidance end of consultation 1. FDA can share with EMA modeling and simulation results once work is done.
Batch 8		
Dabigatran	FDA recommends fully replicated single dose study under fast and fed, the BE limits not wider than 80-125%. EMA recommends 2 single dose studies 1. Fasting study 2. Under conditions of pretreatment of PPI If CV>30%, possible to wider the BE limits follow respective guideline	EMA PSG already finalized. 1. Not allow the BE limits wider than 80-125% because of the safety concern 2. General consideration about inclusion of PPI pretreatment in BE study

Follow up from Wenlei's visit in April 2018 (last PKWP meeting discussion)

Other Batch 9 PSGs

- Aliskiren tablets, FDA and EMA recommendation similar (both fast and fed)
- Octreotide acetate depot, FDA and EMA recommendation similar (single dose, parallel, pAUC similar).
  - EMA lists additional secondary parameter
    - What will you do with the secondary parameter data? Will you have any statistical assessment on the secondary parameter?

GDUFA II Complex Product Workshops

- Oct 2-3, 2017: Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review
  - https://www.fda.gov/Drugs/NewsEvents/ucm554182.htm
- Oct 6th, 2017: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations
  - https://www.fda.gov/Drugs/NewsEvents/ucm552461.htm
- Oct 20th, 2017: Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access
  - https://www.fda.gov/Drugs/NewsEvents/ucm557252.htm
- Jan 9th, 2018: New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products
  - https://www.fda.gov/Drugs/NewsEvents/ucm576064.htm
- Sept 12-13, 2018: Complex Generic Drug Product Development Workshop
  - https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm615104.htm

Future Workshops/Meetings

- **PBPK Modeling for the Development and Approval of Locally Acting Drug Products**
  - ASCPT Pre-Conference
  - Co-Chairs: Liang Zhao (FDA) and Ping Zhao (Gates Foundation)
  - March 13, 2019, Washington DC

- **FY2019 Generic Drug Regulatory Science Initiatives Public Workshop**
  - May 1, 2019
  - FDA White Oak Campus, Silver Spring, MD

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Back-up slides

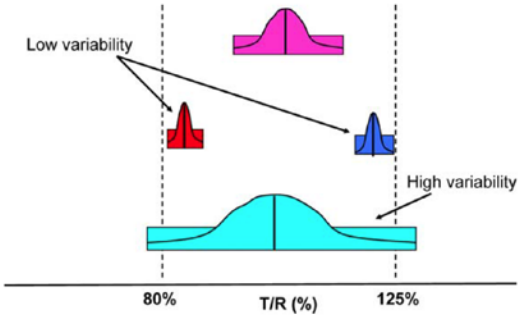
Classification and BE Criteria for NTI Drugs

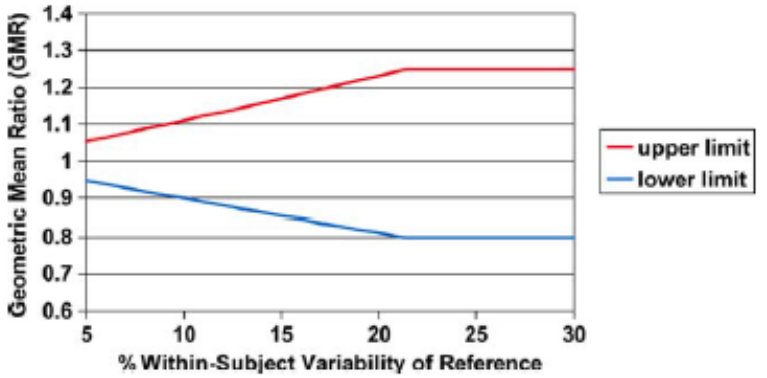
Criteria for NTI classification

1. Little separation between therapeutic and toxic doses or the associated blood/plasma/serum concentrations
2. Sub-therapeutic concentrations may lead to serious therapeutic failure
3. Subject to therapeutic monitoring based on pharmacokinetic (PK) or pharmacodynamic (PD) measures
4. Low-to-moderate (NMT 30%) within-subject variability
5. Doses are often adjusted in small increments (<20%) in clinical practice

BE criteria for NTI drugs (BE = All three criteria passed)

1. Unscaled average BE limits
2. Reference scaled average BE limits (scaled to the variability of the reference product)
3. Comparison of test-to-reference within-subject variability





Clin Pharmacol Ther. 2015 Mar;97(3):286-91. doi: 10.1002/cpt.28. Epub 2014 Dec 15.

Products Classified as NTI in PSGs

Active Ingredient	Route of Administration	Dosage Form	RLD Application No.	Date Recommended
Carbamazepine	Oral	Tablet	16608	Sept 2015
		Tablet, Extended Release	20234	Mar 2015
		Capsule, Extended Release	20712	Mar 2015
		Suspension	18927	Mar 2015
Cyclosporine		Capsule	50625	Apr 2016
		Capsule	50715	Apr 2016
Digoxin		Tablet	20405	Aug 2017
Divalproex Sodium		Tablet, Delayed Release	18723	Dec 2016
		Capsule, Delayed Release Pellets	19680	Dec 2016
		Tablet, Extended Release	21168	Dec 2016
Everolimus		Tablet	21560	Jun 2016
Levothyroxine Sodium		Tablet	21116; 21210; 21301; 21342; 21402	Dec 2014
Phenytoin / Phenytoin Sodium		Tablet, Chewable	84427	May 2017
		Suspension	8762	May 2017
		Capsule, Extended Release	40298	Dec 2014
		Capsule, Extended Release	84349	Dec 2014
Sirolimus		Tablet	21110	Sep 2015
Tacrolimus		Tablet, Extended Release	206406	Jun 2016
		Capsule, Extended Release	204096	Jul 2014
		Capsule	50708	Dec 2012
Valproic Acid		Capsule	18081	Aug 2017
Warfarin Sodium		Tablet	9218	Dec 2012

General Bioequivalence Study Design and Criteria

Study design:
Single dose 2 way crossover

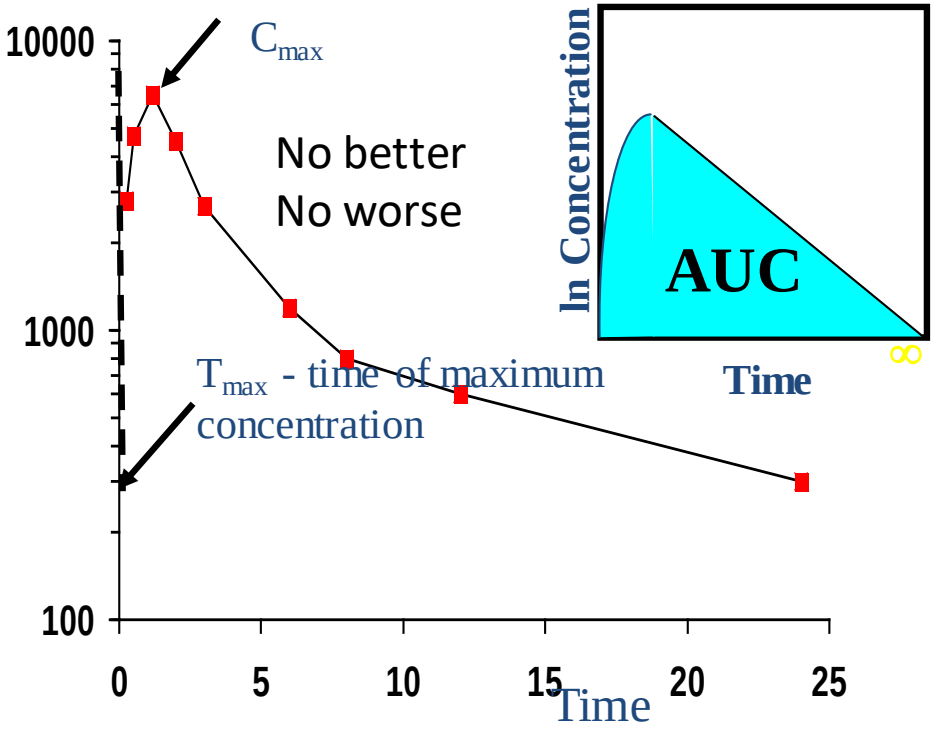
Sequence 1

T – washout period – R

Sequence 2

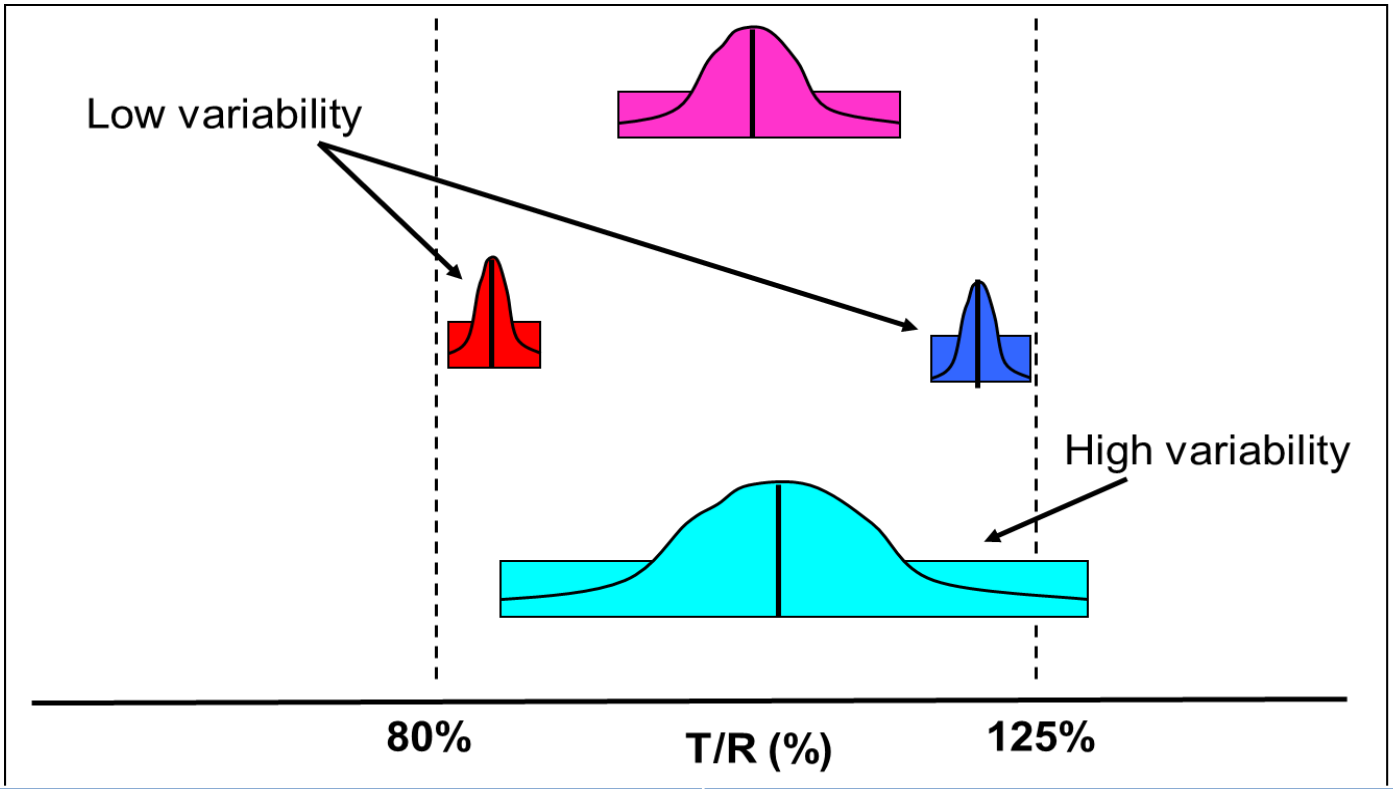
R – washout period – T

- T= Test Drug
- R= Reference Listed Drug (RLD)



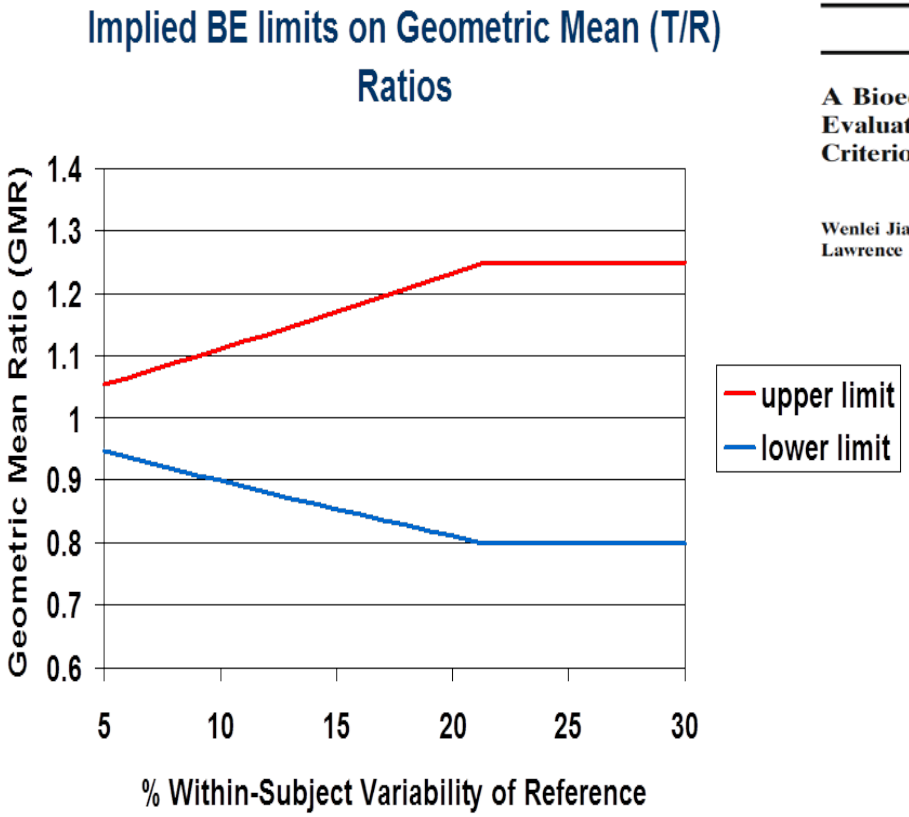
90% confidence interval (CI) for the geometric mean ratio of test/reference within 80.00-125.00%

One Size Bioequivalence Criteria Not Fit All Drugs



Drugs	Within-subject variability (WSV)
NTI drugs	≤ 30%
Highly variable drugs (HVDs)	> 30%

Reference Scaled BE Limits for NTI Drugs



The AAPS Journal, Vol. 17, No. 4, July 2015 (© 2015)
DOI: 10.1208/s12248-015-9753-5

Research Article

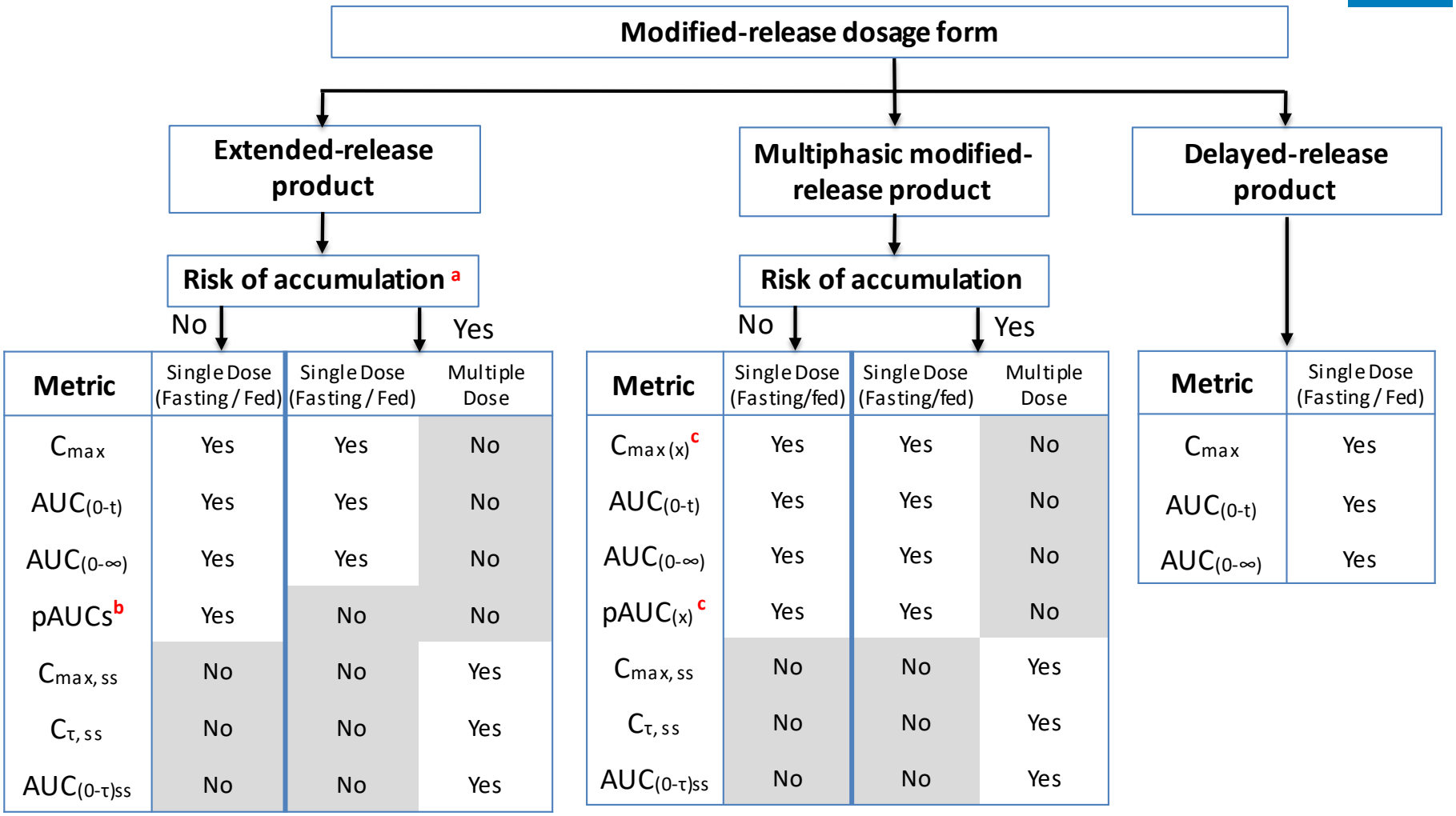
A Bioequivalence Approach for Generic Narrow Therapeutic Index Drugs: Evaluation of the Reference-Scaled Approach and Variability Comparison Criterion

Wenlei Jiang,[1] Fairouz Makhlouf,[2] Donald J. Schuirmann,[2] Xinyuan Zhang,[1] Nan Zheng,[1] Dale Conner,[1] Lawrence X. Yu,[3] and Robert Lionberger[1,4]

CV_{WR}	Reference Scaled BE limits
5	94.87 - 105.41
10	90.02 - 111.08
15	85.35 - 117.02
20	81.17 - 123.20
>21.42	80.00 - 125.00

Warfarin Sodium Product Specific Guidance.
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201283.pdf

EMA BE Guidance _MR dosage form



Metric	Single Dose (Fasting / Fed)	Single Dose (Fasting / Fed)	Multiple Dose
C_{max}	Yes	Yes	No
$AUC_{(0-t)}$	Yes	Yes	No
$AUC_{(0-\infty)}$	Yes	Yes	No
pAUCs [b]	Yes	No	No
$C_{max,ss}$	No	No	Yes
$C_{\tau,ss}$	No	No	Yes
$AUC_{(0-\tau)ss}$	No	No	Yes

Metric	Single Dose (Fasting/fed)	Single Dose (Fasting/fed)	Multiple Dose
$C_{max(x)}$ [c]	Yes	Yes	No
$AUC_{(0-t)}$	Yes	Yes	No
$AUC_{(0-\infty)}$	Yes	Yes	No
$pAUC_{(x)}$ [c]	Yes	Yes	No
$C_{max,ss}$	No	No	Yes
$C_{\tau,ss}$	No	No	Yes
$AUC_{(0-\tau)ss}$	No	No	Yes

Metric	Single Dose (Fasting / Fed)
C_{max}	Yes
$AUC_{(0-t)}$	Yes
$AUC_{(0-\infty)}$	Yes

[a] Single dose with highest strength: "mean $AUC_{(0-\tau)}$ > 90% of mean $AUC_{(0-\infty)}$" is expected as a low extent of accumulation

[b] A representative metric of the shape of the curve (e.g. early $pAUC_{(0-cut\text{-}off\,t)}$ and terminal $pAUC_{(cut\text{-}off\,t\,-\,tlast)}$

[c] $C_{max(x)}$ and $pAUC_{(x)}$ in all phases

GDUFA Science and Research Website

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

CGT (Competitive Generic Therapy)

- The CGT program came into being following the FDA Reauthorization Act 2017 (FDARA) under GDUFA II
- This new approval pathway was created to expedite the development and review of a generic drug for products that lack competition
- A drug can qualify for CGT designation if there is no more than 1 approved drug in the active section of the FDA's Orange Book
- Applicants for drugs with a CGT designation may receive enhanced and expedited review processes of their ANDA
- The Company is eligible for 180 days of CGT exclusivity.
- Under a special forfeiture rule for CGTs, the applicant must commercially market the CGT within 75 days after the date of approval of its ANDA or it will forfeit its exclusivity.

Similarities and Difference Between Generic Drugs and RLD

Generic Drugs and the RLD have the same	Generic Drugs and the RLD may have different
• Active Ingredient • Route of Administration • Dosage Form • Strength • Labeling • Conditions of Use/Patient Population	• Inactive Ingredients • Formulation Design or Drug Release Mechanism • Manufacturing Process

https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/default.htm

Abbreviated Approval Pathways 505(j) & 505 (b)(2)

- **ANDA (505(j))**
  - Application for a duplicate of a previously approved drug product (the reference listed drug (RLD)) that relies on FDA's finding that the RLD is safe and effective
  - Demonstrates sameness to the RLD with respect to active ingredient(s), dosage form, route of administration, strength, previously approved conditions of use, and labeling (with certain exceptions)
  - Includes sufficient information to demonstrate bioequivalence to the RLD
  - May contain certain differences from an RLD as long as investigations are not necessary to establish safety and effectiveness

Draft Guidance for Industry: Determining Whether to Submit an ANDA or a 505(b)(2) Application
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM579751.pdf

Abbreviated Approval Pathways 505(j) & 505 (b)(2)

- **505(b)(2) NDA**
  - Contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference
  - May rely on FDA's finding of safety and/or effectiveness to the extent that the proposed drug product shares characteristics with the listed drug
  - Includes a "bridge" between the proposed drug product and each listed drug that the applicant seeks to rely upon to demonstrate such reliance is scientifically justified

Draft Guidance for Industry: Determining Whether to Submit an ANDA or a 505(b)(2) Application
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Hatch-Waxman Amendments -- The parameters in which we must work

NDA Requirements	ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Microbiology	4. Microbiology
5. Inspection	5. Inspection
6. Labeling	6. Labeling
7. Animal Studies	7. Bioequivalence
8. Clinical Studies	
9. Bioavailability/BE	

- Provides the **legal framework** for generic drug review and approval
- Established **ANDA approval process** based on leveraging the safety and efficacy data from the NDA
- Goals:
  - Create an abbreviated process
  - Reduce the average price paid by consumers/payers
  - Grant patent and exclusivity benefits to drug companies

Especially for complex and modified release products, BE requires an enhanced definition based on solid clinical understanding

Troy DE. FDA.gov [internet] Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendment). [Cited Aug 1. 2013].Accessed at http://www.fda.gov/NewsEvents/Testimony/ucm115033.htm

BE Approaches

- Definition of generic and reference product
- Study design
- PK parameter calculations and BE acceptance limit
- NTI
- Situations in which biowaivers are granted
- Use of BCS for granting waivers